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# Type 1 narcolepsy is not present in 29 HPV-vaccinated individuals with subjective sleep complaints

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## ABSTRACT

**INTRODUCTION:** Human papilloma virus (HPV) vaccine uptake in girls and women is dropping markedly in some countries. Concern about the presumed side effects is the commonest reason why. Reports about side effects include specific sleep complaints such as excessive daytime sleepiness, altered dream activity and periods of muscle weakness. These symptoms are commonly seen in individuals with narcolepsy type 1. We aimed to evaluate whether HPV vaccination was associated with the development of hypocretin-deficient narcolepsy.

**METHODS:** We report the evaluation for sleep disorders, including narcolepsy, in 29 HPV-vaccinated girls and women who were submitted for evaluation of narcolepsy. All were evaluated by polysomnography and the Multiple Sleep Latency Test, and 18 individuals were also evaluated by measures of cerebrospinal fluid hypocretin-1 concentration.

**RESULTS:** None of the 29 girls and women showed signs of narcolepsy type 1.

**CONCLUSION:** Our results do not suggest that an association exists between HPV vaccination and the development of narcolepsy type 1.

**FUNDING:** none.

**TRIAL REGISTRATION:** not relevant.

Human papilloma virus (HPV) vaccine coverage in girls and women has been dropping markedly in some countries [1, 2]. In Denmark, first-dose coverage of the HPV vaccine dropped from around 80% in 2014 to 45% in 2016 [3]. Concern about the presumed side effects is the commonest reason why [4]. It is estimated that more than 0.5 mill Danish girls and women had received HPV vaccination by the end of 2015 [5]. A report from the Danish Health and Medicines Authority in 2015 showed a total of 1,305 reported side effects to the HPV vaccine, including 363 that were assessed as serious [5]. Consequently, many researchers have attempted to determine whether the reported side effects have any association with the HPV vaccine [6-10]. The majority of the studies show no causal relation, and any association remains unverified [11]. However, despite lack of evidence, still fewer girls and women opt for the vaccination [1].

The most frequently reported side effects are injection-site reactions, headache and fatigue [8]. However, we also noted reports of sleep-related symptoms such as excessive daytime sleepiness, dream activity and periods of muscle weakness. These symptoms are commonly seen in individuals with narcolepsy type 1 [12]. This led us to speculate whether HPV vaccination could be associated with the development of narcolepsy type 1. narcolepsy type 1 is a chronic neurological sleep disorder caused by hypocretin deficiency, which is likely due to autoimmune destruction of hypothalamic hypocretinergic neurons [12, 13]. The core symptoms of narcolepsy are excessive daytime sleepiness and signs of rapid eye movement (REM)-sleep dissociation, the most specific being cataplexy. Cataplexy is defined as more than one episode of generally brief (< 2 min.), usually bilateral symmetrical sudden loss of muscle tone with retained consciousness [12, 14]. The development of narcolepsy type 1 has previously been associated with another specific vaccine preparation: the Pandemrix H1N1 vaccine [15, 16]. The other variant of narcolepsy – narcolepsy type 2 – is characterised by normal cerebrospinal fluid; as such there is no loss of hypocretinergic neurons and it is not believed to have an immune system-related pathogenesis. For this reason, we did not include this or any other sleep disorders in the analysis.

We here aimed to evaluate whether sleep-related symptoms following HPV vaccination could be associated with development of narcolepsy type 1. Therefore, we conducted a retrospective case-series study of HPV-vaccinated individuals with specific sleep complaints.

## METHODS

We evaluated 29 girls and women with self-reported sleep complaints after HPV vaccination in a retrospective study. At the time, the Syncope Unit at Bispebjerg-Frederiksberg Hospital was the National Centre for HPV vaccine side-effect in Denmark. The Syncope Unit received the majority of references regarding suspected side effect to the vaccine that were of a degree that required assessment at a hospital department. By the end

## ORIGINAL ARTICLE

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 **TABLE 1**

Characteristics of the girls and women at the time of sleep evaluation.

<b>Anthropometric profiles</b>	
<b>(N = 29)</b>	
Age, yrs, median (range)	21.5 (12.8-32.5)
BMI, kg/m <sup>2</sup> , median (range)	20.3 (16.3-30.4)
<b>HPV vaccine</b>	
<b>(N = 27)</b>	
Time between 1st HPV vaccine dose and polysomnography, yrs, median (range)	4.6 (1.9-7.8)
<b>HPV 6-11-16-18, n (%)</b>	
Brand not specified	21 (77.8)
Gardasil	5 (18.5)
Gardasil and Silgard	1 (3.7)
<b>Questionnaire</b>	
<b>(N = 28)</b>	
Epworth Sleepiness Scale score, median (range)	13 (0-18)
<b>Sleep-related symptoms, n (%)</b>	
<b>(N = 28)</b>	
Fatigue	28 (100)
Fragmented sleep	19 (67.8)
Sleepiness	16 (57.1)
Hypnagogic hallucinations	9 (32.1)
Sleep paralysis	4 (14.2)
Cataplexy	0

HPV = human papilloma virus.

 **TABLE 2**

Results from polysomnography, the Multiple Sleep Latency Test, hypocretin and narcolepsy-associated tissue type.

<b>Polysomnography</b>	
<b>(N = 29)</b>	
Total sleep time, h, median (range)	6.9 (4.0-8.9)
Sleep efficiency, %, median (range)	86.8 (48.8-98.1)
Sleep latency, h, median (range)	0.39 (0.00-1.95)
REM latency, h, median (range)	1.17 (0.41-4.42)
Awakenings, n, median (range)	16 (2-66)
<b>Multiple sleep latency test</b>	
<b>(N = 28)</b>	
Sleep latency, min., median (range)	14.3 (4.4-20.0)
<b>Sudden onset of REM sleep, n (%)</b>	
0/5 sleep periods	15 (53.6)
1/5 sleep periods	9 (32.1)
2/5 sleep periods	3 (10.7)
3/5 sleep periods	1 (3.6)
<b>Cerebrospinal fluid</b>	
<b>(N = 18)</b>	
Hypocretin-1 concentration, pg/ml, median (range)	407 (338-454)
<b>Narcolepsy-associated tissue type</b>	
Positive for tissue type <i>HLA-DQB1*06:02</i> , n (%)	3 (16.7)

REM = rapid eye movement.

of the summer of 2015, more than 600 girls and women had been evaluated at the clinic. Some of them had specific sleep complaints: self-reported fatigue, sleepiness, increased dream activity, fragmented sleep and periodic muscle weakness. Thus, in the period from June 2015 to November 2015, the girls and women with sleep complaints were selected. Out of 187 girls and women evaluated for suspected side effects in this period, 29 had specific sleep complaints. These girls and women were clinically referred to the Danish Centre for Sleep Medicine (DCSM) for sleep evaluation on these criteria. Sleep examinations were conducted from July to November 2015. All participants were evaluated with a focused medical interview and a neurological examination assessing: sleep habits, dream activity, hypnagogic hallucination, sleep paralysis, cataplexy, fatigue and sleepiness including the Epworth sleepiness scale. Further, they were examined with polysomnography (PSG), the Multiple Sleep Latency Test (MSLT), blood tests and lumbar puncture (including *HLA-DQB1\*06:02*, immunoglobulins, cerebrospinal fluid hypocretin-1 (csf-hcrt-1) level) [17]. The PSG and MSLT were done according to the standard procedure in the clinic [17]. Most of the PSG were ambulant, but a few were admitted for the PSG for practical reasons, e.g., due to long transport time.

The diagnostic criteria for narcolepsy type 1 are excessive daytime sleepiness for at least three months and presence of one or both of the following: 1. Cataplexy and a sleep latency (SL) of 8 min. or below and two or more Sleep Onset of REM Periods (SOREMPs); 2. A csf-hcrt-1 concentration below 110 pg/ml [12, 13].

We evaluated data on subjective sleep complaints and from PSG in a retrospective study. All girls and women with self-reported sleep complaints were included in the study and none were excluded. The study was approved by the Danish Health and Medicines Authority.

*Trial registration:* not relevant.

## RESULTS

Characteristics of the 29 girls and women are shown in **Table 1** including sleep-related symptoms reported at medical interview and information about the given HPV vaccine. In addition to the sleep-related symptoms, all girls and women complained of dizziness and 26 (89.7%) of general muscles weakness. Finally, 21 (72.4%) of the girls and women complained of chronic headache and 21 (72.4%) of muscle and joint pain. One girl did not participate in a medical interview, and therefore her symptoms were not characterised. Data on the HPV vaccine given were available for 27 of the girls and women (Table 1). All the girls and women re-

ported symptom onset closely related to the time of their HPV vaccination.

The results of the PSGs are shown in **Table 2**. In general, PSG revealed that all girls and women had a normal distribution of sleep stages, breathing, sinus rhythm and movement pattern. The total sleep time (TST) was less than 6 h in seven of the girls and women.

Results of the MSLTs are shown in **Table 2**. In general, MSLT were normal in 21 girls and women. We found one woman had abnormal changes: 2 SOREMs and a SL of 6 min.; the TST was 6.6 h. Minor abnormalities were found in six women: 1) four girls and women presented with marginal changes in the MSLT; tree had 2-3 SOREMs, but a normal SL of 12-18 min., one had 1 SOREM and a SL of 4 min.; they all had slept more than 6 h during the preceding PSG; and 2) two girls and women had 1 SOREM in the MSLT, with a SL of 8 and 6 min., respectively. However, they had slept less than 6 h during the preceding PSG (5.7 and 5.6 h, respectively). One MSLT was invalid and a repeat was refused.

Csf-hcrt-1 and narcolepsy-associated tissue type were evaluated in 18 girls and women. The results are shown in **Table 2**.

## DISCUSSION

We performed a retrospective analysis of HPV-vaccinated girls and women with specific sleep complaints evaluated for narcolepsy type 1 in June-November 2015 at the DCSM. This was a small study of a highly selected group – 29 girls and women with specific sleep complaints out of 187 evaluated for side effects at the Syncope Unit in the same period. None of the HPV-vaccinated girls and women fulfilled the criteria for a narcolepsy type 1 diagnosis. Despite reports of muscle weakness, none reported cataplexy; and csf-hcrt-1 levels were normal in all of those examined. The study was not designed to assess with epidemiological tools the prevalence of type 1 narcolepsy in the vaccine group compared with the background population. This would have been difficult to do for several reasons. Initially, the vaccination coverage was very high (> 90%), causing the unvaccinated control group to be very small. Also, such data would be biased due to the low prevalence of narcolepsy type 1, the known diagnostic delay, and the fact that many patients are never diagnosed. Instead, we report data from a highly selected group of HPV-vaccinated individuals, who were already under evaluation for side effects and primarily suffered from sleep complaints. If there was any association with narcolepsy type 1, one would expect to identify this association in this particular group of individuals. Consequently, we believe that HPV vaccination is not associated with narcolepsy type 1. The majority of the girls and women's PSG and MSLT were normal.

A few girls and women had marginal changes in their PSG and MSLT, but they all complained of insomnia in the period preceding clinical examination, which is likely to produce false-positive results. Further, short SL in MSLT and SOREM episodes occur in 5% of generally healthy girls and women [18], so these findings should be interpreted with caution. Of those examined, three girls and women (17.6%) were positive for the narcolepsy-associated tissue type: *HLA-DQB1*\*06:02. This result is in line with the prevalence in the general population: 12-38% *HLA-DQB1*\*06:02-positive [12].

One participant showed electrophysiological changes suggestive of narcolepsy type 1; she reported periodic insomnia and excessive daytime sleepiness. She did not present with hypnagogic hallucination, sleep paralysis or cataplexy. She was positive *HLA-DQB1*\*06:02, but so are 12-38% of the population. Csf-hcrt-1 was normal (358 pg/ml). Due to the polysomnographic findings, we kept her as an out-patient in the DCSM and repeated the PSG and MSLT in June 2017. The examinations were completely normal. Further, at follow-up we did two weeks of actigraphy which on average showed a total sleep time of 6 h and 22 min. per day. Our assessment is that the abnormal changes we found in 2015 were caused by sleep deprivation. Follow-up did not raise any suspicion of narcolepsy.

An increased incidence of narcolepsy type 1 was reported after the Pandemrix influenza A (H1N1) vaccination campaign, especially in Finland, Sweden, Norway and Ireland. We therefore consider it important to report that none of the HPV-vaccinated individuals we examined had narcolepsy type 1. There was, on average, a long period (4.6 years) between the time at which the girls and women had received the HPV vaccine and the time at which their sleep evaluations were conducted. They all reported a symptoms onset closely related to time of their HPV vaccination; however, there could be recall bias due to the generally long period. We find it unlikely, though, that the follow-up is too short and that they might develop narcolepsy type 1 at a later point due to their HPV vaccine. All subjects had normal csf-hcrt-1 levels, and as low csf-hcrt-1 is highly sensitive and specific to narcolepsy type 1, this clearly demonstrates that there were no individuals with narcolepsy type 1 in our cohort.

## CONCLUSION

Our results do not suggest that an association exists between HPV vaccination and the development of narcolepsy type 1.

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**CONFLICTS OF INTEREST:** Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

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